

Hartmut Derendorf, Ph.D.

8708 S.W. 42nd Place • Gainesville, FL 32608 • (352) 384-0900, fax (352) 384-0965

November 11, 2004

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Citizen Petition
Docket No. 2004P-0340: Action on Regulation of Generic Transdermal Fentanyl
Delivery System and New Product Approvals for Transdermal Fentanyl

On behalf of Eon Labs, Inc., I would like to respond to the Citizen Petition (Docket No. 2004P-0340) concerning the generic bioequivalence requirements for fentanyl transdermal products. Eon Labs, Inc. has an interest in this Citizen Petition since Eon has submitted an Abbreviated New Drug Application ("ANDA") for a generic fentanyl transdermal system that is bioequivalent to the reference listed drug ("brand"), Duragesic®.

The Citizen Petition requests the Agency to require that bioequivalence of a generic fentanyl transdermal system be performed "*on both intact skin and on skin in which the stratum corneum has been stripped.*"

We feel strongly that this Citizen Petition should be denied. The Citizen Petition lacks merit and the current FDA review standards for ANDA submissions adequately provide for the marketing of therapeutically equivalent generic drug products that have the same safety and efficacy profile as the reference listed drug product (RLD). Current review standards require a bioequivalence study on intact skin as well as a skin irritation and sensitization study (following the FDA Guidance), appropriate chemistry and manufacturing information, and appropriate labeling.

Rationale

Bioequivalence based on both intact skin and on skin in which the stratum corneum has been stripped.

The manufacturer of Duragesic® strongly recommends in its approved labeling that the fentanyl transdermal system should be placed on intact skin and further cautions the patient on the use of agents that might irritate or alter the integrity of the skin:

DURAGESIC® (fentanyl transdermal system) should be applied to non-irritated and non-irradiated skin on a flat surface such as chest, back, flank, or upper arm.

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If the site of DURAGESIC® application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to application.

The intended location for application of the fentanyl transdermal system is on intact skin. The proof of bioequivalence to Duragesic® is therefore adequately achieved by testing the generic equivalent on intact skin. Since the manufacturer of Duragesic® recommends applying the product to intact skin, a bioequivalence study on stripped skin is unnecessary and would put subjects at risk for adverse events using either the brand product, Duragesic® or a generic fentanyl transdermal system.

Rate limiting membrane

The Citizen Petition attempts to show that applying a suboptimal fentanyl transdermal system to the skin, especially to non-intact skin, can be harmful to the patient. The Petition further claims that the existing Duragesic® product is 'intended to provide approximately equal resistance to skin penetration as intact skin'. We concede that if a different transdermal system that did not include a rate limiting membrane was used for a generic product, there might be some concern regarding a theoretical or potential difference in product performance compared to Duragesic®. This concern does not apply to the Eon Labs fentanyl transdermal system, as the Eon drug product is a reservoir system that uses the same type of barrier system and material as the Duragesic® reservoir product. The details are described in Eon's application.

Conclusion

The Citizen Petition wrongly suggests that ANDA approval of a generic drug product for a generic transdermal fentanyl delivery system should be performed on both intact and non-intact skin. The author of the Citizen Petition offers no scientific evidence for performing a bioequivalence study on non-intact skin, only conjecture.

The generic transdermal fentanyl delivery system manufactured by Eon Labs, Inc. is a reservoir system with a release membrane similar to Duragesic®. Eon Labs, Inc. has submitted an ANDA that included a bioequivalence study as well as a skin irritation and sensitization study comparing the Eon product to Duragesic®¹. Moreover, data submitted with Eon's ANDA show that the generic transdermal fentanyl delivery system is bioequivalent to Duragesic® when used according to the approved labeling.

We strongly feel that this Citizen Petition should be denied based in the justification discussed above. The Citizen Petition lacks scientific merit. Moreover, the references cited in this petition contain general information on fentanyl absorption that is not relevant to the argument for performing a bioequivalence study on stripped skin. Finally, the current FDA review standards for ANDA submissions adequately provide for the

¹ Data on file with the Office of Generic drugs/FDA.

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marketing of therapeutically equivalent generic drug products that have the same safety and efficacy profile as the reference listed drug product (RLD).

I appreciate your consideration of my comments and would be happy to answer any questions.

Yours truly,

A handwritten signature in black ink, appearing to read "H. Derendorf". The signature is fluid and cursive, with the first name "H." and the last name "Derendorf" clearly distinguishable.

Hartmut Derendorf, Ph.D.
Distinguished Professor & Chairman
Department of Pharmaceutics
University of Florida

cc: Mr. Gary Buehler
Director, Office of Generic Drugs, CDER
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place HFD 600
Rockville, MD 20855